

Substitute for form 1449A/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	09/787,461
				Filing Date	March 2, 2001
				First Named Inventor	Esteban Cvitkovich
				Art Unit	1614
				Examiner Name	Phyllis Spivack
Sheet	1	of	10	Attorney Docket Number	13566.105002

U.S. PATENT DOCUMENTS					
Examiner Initials *	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code ² (if known)			
		US-20020137663	9/26/2002	Forman et al.	
		US-20040019027	1/29/2004	Forman et al.	
		US- 20040108086	06/10/2004	Takahashi et al.	
		US- 20040002602	01/01/04	Francesch et al.	
		US- 5,089,273	2/18/1992	Rinehart et al.	
		US- 5,149,804	9/22/1992	Rinehart et al.	
		US-5,256,663	10/26/1993	Rinehart et al.	
		US- 5,654,426	8/5/1997	Rinehart et al.	
		US- 5,721,362	2/24/1998	Corey et al.	
		US- 5,908,835	06/01/1999	Bissery	
		US- 5,985,876	11/16/1999	Rinehart et al.	
		US- 6,124,293	9/26/2000	Rinehart et al.	
		US- 7,241,892	07/10/07	Cuevas et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
		WO 00/69862	11/23/2000	Cuevas et al.		
		WO 01/77115	10/18/2001	Flores et al.		
		WO 01/87894	11/22/2001	Cuevas et al.		
		WO 02/064843	8/22/2002	Haygood et al.		
		WO 03/039571	5/15/2003	Jimeno et al.		
		WO 05/49029	06/02/2005	Gianni et al.		

Examiner Signature	/Phyllis Spivack/	Date Considered	06/05/2008
-----------------------	-------------------	--------------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.S./

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 2 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Akers, "Excipient -Drug Interactions in Parenteral Formulations," Journal of Pharmaceutical Sciences, 91(11), pp. 2283-2300, Nov. 2002	
		Biroccio et al., "Telomere Dysfunction Increases Cisplatin and Ecteinasidin-743 Sensitivity of Melanoma Cells," Molecular Pharmacology, 63:632-638 (2003)	
		Blay et al., "Combination of Trabectedin and Doxorubicin for the Treatment of Patients with Soft Tissue Sarcoma: Safety and Efficacy Analysis," 43rd annual ASCO meeting, June 1-5, 2007	
		Bonfanti et al., "Effect of Ecteinasidin-743 on the Interaction Between DNA Binding Proteins and DNA." Anticancer Drug Des. 14, 179-86, 1999	
		Brandon et al., "In-vitro Cytotoxicity of ET-743 (Trabectedin, Yondelis), a Marine Anti-cancer Drug, in the Hep G2 Cell Line: Influence of Cytochrome P450 and Phase II Inhibition, and Cytochrome P450 Induction, Anti-cancer Drugs, 16:935-943 (2005)	
		Burstein et al., "Phase I study of Doxil and Vinorelbine in Metastatic Breast Cancer," Annals of Oncology, vol. 10, pages 1113-1116, 1999, XP8000751	
		Corey et al., "Enantioselective Total Synthesis of Ecteinasidin 743", J. Am. Chem. Soc., 118, 9202-9203, 1996	
		Delaloge et al., "Ecteinasidin (ET-743) in heavily pretreated refractory sarcomas: Preliminary evidence of activity," Eur. J. Cancer, vol. 35, suppl. 4, page S271, Abstract No. 1080, Sept 15, 1999	
		Delaloge, S. et al., "Ecteinasidin-743: A Marine-Derived Compound in Advanced Pretreated Sarcoma Patients-Preliminary Evidence of Activity", J. of Clinical Oncology, vol. 19, no. 5, pp. 1248-1255, 2001	
		DeVita et al., "Combination Versus Single Agent Chemotherapy: A Review of the Basis for Selection of Drug Treatment of Cancer", Cancer, vol. 35, pp. 98-110, 1975	
		D'Incalci et al., "Mode of action of Ecteinasidin-743 (ET-743)," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, pages 3872s-3873s, Abstract of Plenary Session 7, November 16-19, 1999	
		D'Incalci et al., "The Combination of ET-743 and Cisplatin (DDP): From a Molecular Pharmacology Study to a Phase I Clinical Trial," from the AACR Annual Meeting of April 6-10, 2002, Abstract 404	
		D'Incalci et al., "In human tumor xenografts the resistance to ET-743 or to cisplatin can be overcome by giving the two drugs in combination," European Journal of Cancer, 38, Suppl. 7, 34 (November 2002)	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 3 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		D'Incalci et al., "Preclinical and Clinical Results with the Natural Marine Product ET-743," Expert Opin. Investig. Drugs, 12(11):1843-1853 (2003)	
		D'Incalci et al., "The combination of yondelis and cisplatin is synergistic against human tumor xenografts," European Journal of Cancer 39: 1920-1926 (2003)	
		Donald et al., "Complete Protection By High-Dose Dexamethasone Against The Hepatotoxicity of the Novel Antitumor Drug Yondelis (ET-743) in The Rat," Cancer Research, Vol. 63, p. 5902-5908, September 2003	
		Donald et al., "Dietary Agent Indole-3-Carbinol Protects Female Rats Against the Hepatotoxicity of the Antitumor Drug ET-743 (trabectedin) Without Compromising Efficacy in a Rat Mammary Carcinoma" International Journal Of Cancer, Vo1. 111, No.6, p. 961-967, 2004	
		Dorr and Van Hoff, "Doxorubicin," Cancer Chemotherapy Handbook, 1994, pp. 395-416	
		"Doxil (doxorubicin HCl Liposome Injection) Product Information", October 10, 2004, pages 1-16, XP002389462, <<web.archive.org/web/20041009180>>	
		Eckhardt et al., "In vitro Studies of a Novel Marine Cytotoxic, Ecteinascidin (ET-743)," New Drugs and Pharmacology, Annals of Oncology, 7 (Suppl. 5), 131, Abstract 632P (1996)	
		Endo et al., "Total Synthesis of Ecteinascidin 743", J. Am. Chem. Soc., 124, 6552-6554, 2002	
		Erba et al., "Synergistic cytotoxic effect of ET-743 and cisplatin," Clinical Cancer Research, Vol. 6, Abstract 209, November 7-10, 2000	
		Erba et al., "Combination of yondelis (ET-743) and oxaliplatin in experimental ovarian cancer," from the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics of Nov. 17-21, 2003, Abstract C247	
		Erba et al., "ET-743 and Cisplatin (DDP) Show in Vitro and in Vivo Synergy Against Human Sarcoma and Ovarian Carcinoma Cell Lines," from the AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics of October 29 – November 2, 2001, Abstract 406.	
		Erlichman, C., "18: Pharmacology of Anticancer Drugs, "The Basic Science of Oncology, 2nd edition, Tannock et al., editors, McGraw-Hill, New York, pages 317-337, 1992	
		European Medicines Agency (EMA), "Scientific Discussion" from the European Public Assessment Report for Yondelis®, Revision 1, published March 31, 2008, downloaded from the internet on April 2, 2008, from the website << http://www.emea.europa.eu/humandocs/Humans/EPAR/yondelis/yondelis.htm >>	
		FDA approved label for Pharmacia and Upjohn's Doxorubicin Hydrochloride for Injection (May 8, 2003)	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 4 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Faircloth et al., "In Vivo Combinations of Chemotherapeutic Agents with Ecteinascidin 743 (ET743) Against Solid Tumors," from the Proceedings AACR-NCI-EORTC of November 2001, Abstract 387	
		Faircloth et al., "Dexamethasone Potentiates the Activity of Ecteinascidin 743 in Preclinical Melanoma and Osteosarcoma Models," Abstract and Presentation 379 (2002)	
		Faulkner et al., "Symbiotic Bacteria in Sponges: Sources of Bioactive Substances," Drugs from the Sea, Fusetani, N. (ed.), Basel Karger, 2000, pp. 107-119	
		Fayette et al., "ET-743: a Novel Agent with Activity in Soft-Tissue Sarcomas," Current Opinion in Oncology, 18:347-353 (2006)	
		Friereich et al., "Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man," Cancer Chemotherapy Reports, 50:4, May 1966, pp.219-245	
		Fukuyama et al., "Total Synthesis of Saframycin A," J. Am. Chem. Soc., 112, 3712-3713, 1990	
		Fukuyama et al., "Stereocontrolled Total Synthesis of Saframycin B," J. Am. Chem. Soc., 104, 4957-4958, 1982	
		Garcia-Carbonero et al., "Population pharmacokinetics of ecteinascidin 743 in patients with advanced soft tissue sarcoma," Clinical Cancer Research, vol. 6, Supplement, Abstract 211, page 4508s, NCI-EORTC-AACR Symposium On New Drugs In Cancer Therapy, November 7-10, 2000	
		Ghielmini, M. et al., "In vitro schedule-dependency of myelotoxicity and cytotoxicity of Ecteinascidin 743 (ET-743)," Annals of Oncology, vol. 9, pages 989-993, 1998	
		Gianni et al. "Definition of the Least Toxic Sequence and Optimal Therapeutic Dose of Yondelis® in Combination with Doxorubicin in Patients with Untreated Metastatic Soft Tissue Sarcomas and Advanced Pre-Treated Anthracycline," Clinical Cancer Research, Vol. 9, No. 16, pg. 6081S (December 2003)	
		Giovanna et al., "Importance of DNA repair mechanisms for the sensitivity of tumor cells to ET-743," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3790s, Abstract 303, November 16-19, 1999	
		Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, page 36, 1975	
		Gore et al., "Phase I Combination Study of Trabectedin and Capecitabine in Patients With Advanced Malignancies," Poster Presentation, 42nd ASCO Annual Meeting held on June 2-6, 2006, Atlanta, Georgia	
		Grever et al., "The National Cancer Institute: Cancer Drug Discovery and Development Program", Seminars in Oncology, vol. 19, no. 6, 622-638, December 1992	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 5 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Grosso et al., "Steroid Premedication Markedly Reduces Liver and Bone Marrow Toxicity of Trabectedin in Advanced Sarcoma," European Journal of Cancer 42:10, 1484-1490 (2006)	
		Holmes, "Paclitaxel Combination Therapy in the treatment of Metast Breast Cancer: A Review," Seminars in Oncology, vol. 23, pp. 46-56, 1996	
		Hornicek et al., "In vitro effect of the tetrahydroisoquinoline alkaloid Ecteinascidin-743 (ET-743) on chondrosarcoma (CHSA) cells," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3790s, Abstract 304, November 16-19, 1999	
		Hornicek et al., "Effect of Ecteinascidin-743 and Plasminogen related Protein B on a Human Chondrosarcoma Xenograft Tumor in Mice," Clinical Cancer Research, Vol. 7 Supplement P3734S-3734S, Abstract 398 (November 2001)	
		Ishikawa et al., "Tumor Selective Delivery of 5-Fluorouracil by Capecitabine," Biochemical Pharmacology, vol. 55, pp. 1091-1097, 1998	
		Jimeno et al., "Pharmacokinetics (PK)/Pharmacodynamic (PD) Relationships in Patients (PT) Treated With Ecteinascidin-743 (ET-743) Given As 24 Hours Continuous Infusion (CI)," Journal of Clinical Oncology, ASCO Annual Meeting Proceedings, Abstract No. 744, May 15-18, 1999	
		Jimeno, Jose et al., "Adding Pharmacogenomics to the Development of New Marine-Derived Anticancer Agents," Journal of Translational Medicine, volume 4, issue 3, January 9, 2006, downloaded from the internet website: << http://www.translational-medicine.com/content/4/1/3 >>	
		Jin et al., "The antitumor agent Ecteinascidin 743 (ET743), inhibits transcriptional activation of the MDR1 Gene by multiple inducers," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3790s, Abstract 302, November 16-19, 1999	
		Jin et al., Ecteinascidin-743, A Transcription-Targeted Chemotherapeutic that Inhibits MDR I Activation. Proc. Natl. Acad. Sci. USA, 97, 6775-9, 2000	
		Kanzaki et al., "Activity of Ecteinascidin 743 and Synergism with Doxorubicin and Vincristine in P-Glycoprotein/MDR1 Over-Expression Cell Lines," from the Proceedings of the AACR, Vol. 42, Abstract 4354 (March 2001)	
		Kanzaki et al., "Microsatellite Instability (MSI) Induced by Ecteinascidin743 and Protection with Aspirin," from the 93rd Annual Meeting of the American Association for Cancer Research, Abstract 5382 (April 6-10, 2002), Vol. 43, March 2002, page 1087	
		Kovalcik et al., "The Stability of Cyclophosphamide in Lyophilized Cakes. part I. Mannitol, Lactose, and Sodium Bicarbonate as Excipients," Journal of Parenteral Science and Technology, vol. 42, no. 1, Jan-Feb. 1988, pp. 29-37	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.S./

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 6 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Laverdiere et al., "Phase II Study of Ecteinascidin 743 In Heavily Pretreated Patients with Recurrent Osteosarcoma", Cancer, American Cancer Society, Philadelphia, PA, August 15, 2003, vol. 98:4, pages 832-840, XP002314512	
		Leonetti et al., "Antitumoral Effect of the G-quadruplex Interactive Compound RHPS4 on Human Melanoma Cells Possessing Relatively Long Telomeres," from the Proceedings of the AACR, Volume 45, March 2004	
		Lopez-Lazaro et al., "Exploratory evaluation of the potential predictors for dose-limiting toxicities (DLTs) in patients treated with Ecteinascidin-743 (ET-743) as a 24-h intravenous (iv) infusion every 3 weeks and its relationship to pharmacokinetics (PK)," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3791s, Abstract 308, November 16-19, 1999	
		Lyass et al., "Phase I Study of Doxil-Cisplatin Combination Chemotherapy in Patients with Advanced Malignancies," Clinical Cancer Research, vol. 7, pages 3040-3046, October 2001, XP0086753	
		Maier et al., "In vitro inhibition of endothelial cell growth by the antiangiogenic drug AGM-1470 (TNP-470) and the antiendoglin antibody TEC-11," Anti-Cancer Drugs, vol. 8, pp. 238-244, 1997	
		Magro et al., "The Role of PARP and PARP Inhibitors in Yondelis (Trabectedin) Mediated Cytotoxicity," Abstract and Presentation from the AACR Annual Meeting, April 17, 2007	
		Manzanares et al., "Advances in the Chemistry and Pharmacology of Ecteinascidins, A Promising New Class of Anticancer Agents," Curr. Med. Chem. - Anti-Cancer Agents, 2001, vol. 1, pp. 257-276	
		Martinez et al., "Phthalascidin, A Synthetic Antitumor Agent with Potency and Mode of Action Comparable to Ecteinaseidin 743." Proc. Natl. Acad. Sci. USA 96; 3496-501, 1999	
		Martinez, E. J. et al., "A New, More Efficient, and Effective Process for the Synthesis of a Key Pentacyclic Intermediate for Production of Ecteinascidin and Phthalascidin Antitumor Agents." Org. Lett. 2, 993-6, 2000	
		McLeod, "Clinically relevant drug-drug interactions in oncology," Br. J. Clin. Pharmacol., 45:539-544 (1998).	
		Meco et al., "Effective combination of ET-743 and doxorubicin in sarcoma: preclinical studies," Cancer Chemother. Pharmacol. 52: 131-138 (2003).	
		Meco et al., "The combination of ET-743 and Irinotecan is active in preclinical models in rhabomyosarcoma," presented at the 16th EORTC-NCI-AARC Symposium on Molecular Targets and Cancer Therapeutics held in Geneva on September 28 - October 1, 2004.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet

7

of

10

Complete if Known

Application Number

09/787,461

Filing Date

March 2, 2001

First Named Inventor

Esteban Cvitkovich

Art Unit

1614

Examiner Name

Phyllis Spivack

Attorney Docket Number

13566.105002

NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Menchaca et al., "Synthesis of Natural Ecteinascidins (ET-729, ET-745, ET-759B, ET-736, ET-637, ET-594) from Cyanosafracin B," J. Org. Chem., published on web October 21, 2003, pp. 8859-8866	
		Merck Manual on-line edition version, "Types: Overview of Cancer," 4 pages, downloaded from internet website << http://www.merck.com/mmhe >>, February 2003	
		Minuzzo, M. et al., "Interference of Transcriptional Activation by the Antineoplastic Drug Ecteinascidin.743." Proc. Natl. Acad. Sci. USA 97, 6780-4, 2000	
		Moore et al., "Sequencing evaluation of ET-743 combinations with standard chemotherapy agents against a panel of human tumor cell lines," Clinical Cancer Research, Vol. 6, Abstract 504 (November 2000)	
		Morioka et al., "Antiangiogenesis Treatment Combined with Chemotherapy Produces Chondrosarcoma Necrosis," Clinical Cancer Research, Vol. 9, 1211-1217, March 2003	
		Pharma Mar Press Release, "YONDELIS(r) STS-201 Efficacy and Safety Data Presented at ASCO 2007" Pharma Mar Grupo Zeltia, << http://www.pharmamar.com/en/press >>, June 5, 2007	
		Pharma Mar Press Release, "The European Commission Authorizes YONDELIS(r) Commercialization for Soft Tissue Sarcoma" Pharma Mar Grupo Zeltia, << http://www.pharmamar.com/en/press >>, September 20, 2007	
		Pommier et al., "DNA Sequence- And Structure-Selective Alkylation of Guanine N2 in the DNA Minor Groove by Ecteinascidin 743, a Potent Antitumor Compound from the Caribbean Tunicate Ecteinascidia Turbinata." Biochemistry 35, 13303-9, 1996	
		Rinehart, K.L., "Antitumor Compounds from Tunicates." Med. Res. Rev. 20, 1-27, 2000	
		Riccardi et al., "Preclinical Activity and Biodistribution of Ecteinascidin 743 (ET-743) and Doxorubicin (DOX) Combinations in Human Rhabdomyosarcoma," from the AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics of October 29 – November 2, 2001, Abstract 405	
		Riccardi et al., "Effective Combinations of ET-743 and Doxorubicin for Tumor Growth Inhibitions Against Murine and Human Sarcomas in Athymic Mice," from the Proceedings of the AACR, Vol. 42, Abstract 1132 (March 2001)	
		Riccardi et al., "Combination of trabectedin and irinotecan is highly effective in a human rhabdomyosarcoma xenograft," Anti-Cancer Drugs, 16:811-815 (2005).	
		Robert et al., "Pharmacokinetics of Doxorubicin in Sarcoma Patients," Eur. J. Clin. Pharmacol., vol. 31, pp. 695-699, 1987	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 8 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Rosing et al., "Pharmacokinetics (PK) of Ecteinascidin-743 (ET-743) in three different phase I trials," Proceedings of the American Association for Cancer Research, vol. 40, pp 81, abstract no. 542, March 1999	
		Ryan, D.P. "Studies with Ecteinascidin-743 (ET-743) A Marine Alkaloid," Cancer Invest, vol. 18 (suppl 1), pp 112, abstract no. 87, January 2000, from the Chemotherapy Foundation Symposium XVII Innovative Cancer Therapy for Tomorrow, November 3-6, 1999, New York, NY	
		Ryan, DP et al., "Phase I and Pharmacokinetic Study of Ecteinascidin-743 Administered as a 72 hours Continuous Intravenous Infusion in Patients with Solid Malignancies", Clinical Cancer Research, Vol. 7, pp. 231-242, 2001	
		Saito et al., "Synthesis of Saframycins- 3," J. Org. Chem., 54, 5391, 1989	
		Sakai et al., "Additional Antitumor Ecteinascidins from a Caribbean Tunicate: Crystal Structures and Activities in vivo," Proc. Natl. Acad. Sci., vol. 89, Dec. 1992, pp. 11456-11460	
		Sato et al., "Multicenter Phase II Trial of Weekly Paclitaxel for Advanced or Metastatic Breast Cancer: the Saitama Breast Cancer Clinical Study Group (SBCCSG-01)," Japanese Journal of Clinical Oncology, Vo. 33, no. 8, pp. 371-376, August 2003	
		Scotlandi et al., "Effectiveness of Ecteinascidin-743 against Drug-sensitive and -resistant Bone Tumor Cells," Clinical Cancer Research, 8:3893-3903 (December 2002)	
		Scotto et al., "Ecteinascidin 743, a novel chemotherapeutic agent that targets transcriptional activation of a subset of genes, including MDR1," Clinical Cancer Research, vol. 6, Supplement, Abstract 210, page 4508s, NCI-EORTC-AACR Symposium On New Drugs In Cancer Therapy, November 7-10, 2000	
		Sessa et al., "Trabectedin for Women with Ovarian Carcinoma After Treatment with Platinum and Taxane Fails," Journal of Clinical Oncology, vol. 23, no. 9, pp. 1867-1874, March 20, 2005	
		Shertzer et al., "Protection Against Carbon Tetrachloride Hepatotoxicity by Pretreatment with indole-3-carbinol," Exptl. Molec. Pathol., vol. 46, pp. 180-189 (1987)	
		Shertzer et al., "Protection from N-Nitrosodimethylamine Mediated Liver Damage by Indole-3-carbinol," Exptl. Molec. Pathol., vol. 47, pp. 211-218 (1987)	
		Smyth, "Rationale for Drug Combinations," European Journal of Cancer, 39, 1816-1817 (2003)	
		Taamma et al., "Ecteinascidin-743 (ET-743) 24 hour continuous intravenous infusion (CI) phase I study in solid tumors (ST) patients (pts)." Proceedings of the American Association for Cancer Research, vol. 39, pp 323, abstract no. 2207, March 1998	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 9 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Taamma et al., "Ecteinascidin-743 (ET-743) in heavily pretreated refractory sarcomas: early results of the French experience," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3791s, Abstract 309, November 16-19, 1999	
		Taamma et al., "Phase I and Pharmacokinetic Study of Ecteinascidin-743, a New Marine Compound, Administered as a 24 hours Continuous Infusion in Patients with Solid Tumors", J. of Clinical Oncology, vol. 19, no. 5, pp. 1256-1265, March 1, 2001	
		Tabor et al., "Anti oxidation Potential of Indole Compounds-Structure Activity Studies," Biological Reactive Intermediates IV, p. 833-836, 1990	
		Takebayashi et al., "Poisoning of Human DNA Topoisomerase I by Ecteinascidin 743, An Anticancer Drug That Selectively Alkylates DNA in the Minor Groove." Proc. Natl. Acad. Sci. USA 96, 7196-201 1999	
		Takebayashi et al., "Multidrug Resistance Induced by DNA Minor Groove Alkylation of Ecteinascidin 743 (Et743)," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3851s, Abstract 602, November 16-19, 1999	
		Takebayashi et al., "Nucleotide excision repair-dependent cytotoxicity of Ecteinascidin 743," Clinical Cancer Research, vol. 6, Supplement, Abstract 207, page 4508s, NCI-EORTC-AACR Symposium On New Drugs In Cancer Therapy, November 7-10, 2000	
		Takahashi et al., "Ecteinascidin 743 (ET-743) and doxorubicin produce synergistic cytotoxic effects in soft tissue sarcoma lines HT-1080 and HS-18," Clinical Cancer Research, Vol. 6, Abstract 208, November 7-10, 2000	
		Takahashi et al., "Sequence-dependent Enhancement of Cytotoxicity Produced by Ecteinascidin 743 (ET-743) with Doxorubicin or Paclitaxel in Soft Tissue Sarcoma Cells," Clinical Cancer Research, 7: 3251-3257 (October 2001)	
		Takahashi et al., "Sequence-dependent Synergistic Cytotoxicity of Ecteinascidin-743 and Paclitaxel in Human Breast Cancer Cell Lines in Vitro and in Vivo," Cancer Research, 62: 6909-6915 (Dec. 1, 2002)	
		Ten Hagen et al., "Pegylated Liposomal Tumor Necrosis Factor-Alpha Results in Reduced Toxicity and Synergistic Antitumor Activity after Systemic Administration in Combination with Liposomal Doxorubicin (Doxil) in soft tissue Sarcoma-Bearing Rats," Int. J. Cancer, vol. 97, pages 115-120, 2002	
		Twelves et al., "A Phase I and Pharmacokinetic (PK) study of Et-743 evaluating a 3 hours (h) intravenous (iv) infusion (I) in patients (pts) with solid tumors," Clinical Cancer Research, Abstract #307, 5 (11, suppl. 3790S-3791S), November 16-19, 1999	
		Twelves et al., "Phase I Trials with ET-743, a marine derived (MD) anticancer agent," Eur. J. Cancer, vol. 35, suppl. 4, page S283, Abstract No. 1135, Sept 15, 1999	

Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 10 of 10

Complete if Known

Application Number	09/787,461
Filing Date	March 2, 2001
First Named Inventor	Esteban Cvitkovich
Art Unit	1614
Examiner Name	Phyllis Spivack
Attorney Docket Number	13566.105002

NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		van Kesteren et al., "Pharmacokinetics and Pharmacodynamics of the Novel Marine-derived Anticancer Agent Ecteinascidin 743 in a Phase I Dose-finding Study," Clinical Cancer Research, vol. 6, pages 4725-2732, December 2000	
		van Kesteren et al. "Clinical Pharmacology of the Novel Marine-derived Anticancer Agent Ecteinascidin 743 Administered as a 1- and 3-h Infusion in a Phase I Study," Anti-Cancer Drugs, Vol. 13, No.4, pgs. 381-393, April 2002	
		van Kesteren et al. "Yondelis® (trabectedin, ET-743): The Development of an Anticancer Agent of Marine Origin" Anti-Cancer Drugs, Vol. 14, No.7, pgs. 487-502, August 2003	
		Villalona-Calero, M. et al., "A phase I and pharmacokinetic study of ET-743, a novel DNA minor groove binder of marine origin, administered as a 1-hour infusion daily x 5 days," Annals Oncology, Abstract 453, 1998	
		Weiwei et al., "Potent antitumor activity of ET-743 against human soft tissue sarcoma cell lines," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, volume 5, Supplement, page 3790s, Abstract 305, November 16-19, 1999	
		Wiesenthal, "Is one 'sensitive' drug better than another?" downloaded from internet website << http://weisenthal.org/feedback.html >>, Feb. 4, 2002	
		Wright et al., "Antitumor Tetrahydroisoquinoline Alkaloids from the Colonial Ascidian Ecteinascidia Turbinata", J. Org. Chem., vol. 55, pp. 4508-4512, 1990	
		Zepek et al., "Preliminary results of phase II study of ecteinascidin (ET-743) with the 24 hour (H) continuous infusion (CI) q3week schedule in pretreated" Clinical Cancer Research, vol. 6, Supplement, Abstract 212, pages 4508s-4509s, NCI-EORTC-AACR Symposium On New Drugs In Cancer Therapy, November 7-10, 2000	
		Zewail-Foote et al., "Ecteinascidin 743: A Minor Groove Alkylator that Bends DNA Toward the Major Groove," J. Med. Chem. 42, 2493-7, July 15, 1999	

Examiner
Signature

/Phyllis Spivack/

Date
Considered

06/05/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.